



BIOMEDICAL INSTRUMENTATION
& TECHNOLOGY

Radiation Sterilization Failures
What Can Go Wrong?

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About the Author



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Medical device manufacturers must choose a sterilization process for their devices before they go to market. There are several types of sterilization process, but one of the two most common forms is radiation. (The other is ethylene oxide.)

With the international ANSI/AAMI/ISO 11137-1 and 11137-2 standards governing development, validation, and routine control of radiation sterilization, manufacturers can readily implement the appropriate practices for radiation sterilization into their manufacturing process.

Once the sterilization dose is established, the manufacturer has to demonstrate that this dose can be delivered consistently to the product and monitor the sterilization process routinely to confirm that this has been achieved.

Occasionally products will fail an initial sterilization dose establishment or a sterilization dose audit. When that happens, it can slow or stop production. The first thing to remember is all failures are different. There is no benefit in jumping to conclusions or making quick assumptions and guesses.

Manufacturers can identify and correct failures when they approach them properly, and can always consult with a testing laboratory if they have questions regarding a failure. Here is a list of the most common causes of failures and a brief description of how to combat them.

1. **Increased bioburden count.** This occurs when, for any reason, the bioburden count results are higher than during the initial

sterilization dose establishment. In this case, manufacturers can investigate and discover where they are getting the extra bioburden and fix the problem or they can re-establish the sterilization dose.

2. **Increased bioburden resistance.** When the bioburden count remains the same, but more radiation-resistant microorganisms are present later on, the device has increased bioburden resistance. To correct the problem, once again device-makers can either find the source of the increased radiation-resistant microorganisms in the assembly process and fix it or re-establish the radiation dosage.
3. **Bioburden underestimation.** In this situation, there are actually more microorganisms on the product than the bioburden test results indicate. Testers can repair this by performing a more extensive recovery efficiency test to determine the proper bioburden count and radiation dosage or may include using a different bioburden test method to increase the test sensitivity.
4. **Contamination during testing.** Some devices need a lot of manipulation during sterility testing. The most common manipulations are disassembly and cutting performed to expose fully all the critical surfaces to the test medium. If testers do this after delivery of the verification dose and during the test of sterility, the manipulation can introduce microorganisms. The best approach is to prepare product items (i.e.

After completing a bioburden extraction, a Nelson Labs study director filters the solution to grow the microorganisms and obtain a bioburden count.



perform the necessary manipulations) prior to delivery of the verification dose.

5. **Shipping etiquette.** Once the sterilization outsourcers irradiate the product items, the outside of the packaging can become contaminated during shipping. This can introduce microorganisms into the sterility test environment. To prevent this, provide multiple barriers in dosing and shipping by lining the shipper box with two plastic bags before placing the product items into the box.

A couple of lesser common causes of failures include compromised packaging or incorrect dosing. These causes, along with numbers four and five above, are not *true* failures, meaning that the sterility growth is not due to microorganisms surviving the radiation dose. If manufacturers investigate and implement corrective action, they can repeat the test and use the repeat results in the dose establishment or sterilization dose audit.

Establishing the Dose

There are three methods a testing laboratory uses to establish a radiation sterilization dose: Verification Dose Maximum (VD_{max}), Method 1 and Method 2.

- Manufacturers select the VD_{max} radiation approach most frequently. Not coincidentally, it is also the most cost effective. This approach determines for manufacturers if they can sterilize their medical device with the most typical radiation dose—25kGy. The

method requires a bioburden determination on 30 product items, 10 each from three different batches. There is a maximum bioburden limit that applies in order to use this method. The laboratory uses the results of the bioburden test in a table from ANSI/AAMI/ISO 11137-2 to determine the appropriate verification dose. They apply this verification dose to 10 additional product items from one batch followed by a test of sterility on the irradiated product items.

If one or fewer product items tests positive for microorganism growth, the sterilization dose is substantiated. The laboratory must perform additional testing if there are two positives. If three or more of the product items test positive for growth, the sterilization dose is not substantiated. In the case of a failure in substantiation, manufacturers must implement corrective action (e.g., make changes to the device manufacturing process to reduce the bioburden) and try again or use another method to establish the sterilization dose.

VD_{max} also has tables for substantiation of other, less often used, sterilization doses (i.e. 15.0, 17.5, 20.0, 22.5, 27.5, 30.0, 32.5, and 35 kGy) in AAMI TIR33.

- Method 1 is a great choice for establishing the sterilization dose if manufacturers find they need to use a lower dose of radiation because of the radiation compatibility of materials comprising their device or if a sterility assurance level (SAL) other than 10^{-6} is necessary (e.g., 10^{-3} or 10^{-4}). Different materi-

als react differently to radiation and subjecting them to higher doses can be harmful. They may need a lower dose that corresponds more closely with their product's bioburden. Method 1 for dose establishment follows a similar testing scheme as VD_{max} , but the laboratory completes the test of sterility on 100 product items after exposure to the verification dose instead of 10. To do this, the laboratory determines the verification dose using a different table from ANSI/AAMI/ISO 11137-2.

Out of the 100 product items tested for sterility, the verification is accepted if two or fewer product items test positive for growth and the sterilization dose can be read from the table in ANSI/AAMI/ISO 11137-2. If three or more product items test positive, manufacturers need to implement corrective action (e.g., make changes to their manufacturing process to reduce the bioburden) and try again or use another approach to establish the sterilization dose. Because of the larger sample size, Method-1 validation is more costly than VD_{max} .

- Method 2, the most infrequently selected method of establishing the sterilization dose, determines the lowest dose of radiation possible to sterilize the device. It does not use an established dosing table. Instead it determines the radiation resistance of the bioburden by using multiple radiation doses (incremental dosing) on a number of product items (groups of 60 product items receiving eight or nine different doses) to determine at

which dose negative tests of sterility are obtained from the irradiated product items. These data are used to calculate a verification dose which is applied to an additional 100 product items. The appropriate sterilization dose is then determined by calculation using defined equations.

Once the dose establishment process is complete, manufacturers don't need to repeat the process of establishing the sterilization dose unless they make a change to the device or manufacturing process. However, a periodic sterilization dose audit is required (usually quarterly) for all methods of establishing the sterilization dose. Sterilization dose audits ensure the established radiation dosage remains appropriate. Changes in assembly processes, device composition, and assembly environment can affect the bioburden and potentially necessitate a change in sterilization dose.

Choosing the Appropriate Method

A credible laboratory will offer the manufacturer guidance and advice on what method of establishing the sterilization dose that will work best. When manufacturers know the three dose establishment methods and the most common causes of failures and their differences, they are more prepared to make educated decisions that will benefit their organizations and speed their device approvals in the following ways:

- **Development decisions.** If manufacturers understand the radiation dose likely needed for their device sterilization at the beginning of development, it allows them to pick composition materials that can handle radiation without damage or degradation. They can plan for the lowest cost method.
- **Radiation dose.** Different devices can handle different amounts of radiation. When manufacturers understand the range of radiation levels their device can handle, it makes it easier for sterilization outsourcers to guarantee they can hit the range.
- **Planning.** If device makers know the general radiation sterilization requirements up front, it allows them to plan for product items, sterilization costs and processes well in advance of the product's release. ■



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